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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/556,466	04/21/2000	Benjamin G. Davis	3290.008US1	6782

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EXAMINER

PATTERSON, CHARLES L JR

ART UNIT PAPER NUMBER

1652

DATE MAILED: 04/17/2002 //

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/556,466

Applicant(s)

DAVIS ET AL.

Examiner

Charles L. Patterson, Jr.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 9/4/01 & 2/11/02.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-158 is/are pending in the application.
- 4a) Of the above claim(s) 74-145, 150-152 and 156-158 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-73, 146-149 and 153-155 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 21 April 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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Applicant's election without traverse of Group 19 in Paper No. 10 is acknowledged. Applicants state that this group includes "claims 1-6, 29-26, 37-41, 56-63, 146-147 and 153-54". A careful review of the claims as now presented indicates that the group should include claims 1-73, 146-149 and 153-155 and these claims will be examined as to a hydrolase only.

Claims 74-145, 150-152 and 156-158 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 10.

The disclosure is objected to because of the following informalities:

Throughout the specification and in several of the figures the abbreviation "SBL" is used but is apparently not defined anywhere. Apparently "SBL" is the abbreviation for "subtilisin" and should be defined at least in the first instant of its use, e.g. on page 4, line 9.

On page 18, line 5, the description of Figure 19 lacks a verb. Perhaps "is a" should be inserted between "19" and "plot".

Appropriate correction is required.

Claims 11-12, 14, 16, 18, 19, 34-35, 48-49, 51, 53, 55, 59-60, 72, 146 and 153 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Mo Claims 11, 12, 14, 16, 18, 48, 49, 51, 53 and 55 are indefinite in the recitation of "Protein Data Bank entry...". Accession numbers can change and therefore the instant term is indefinite. Giving the source of the enzyme or some other characteristic might be used instead of the instant recitations.

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In addition, claim 53 omits the accession number, the closing parenthesis and the words ", where the reference residue is at or near a residue selected from the group consisting of".

Claim 19 is indefinite in the recitation of "said target" in that there is no antecedent basis for this term. Substituting "said target molecule" for the instant recitation would overcome this rejection.

Claim 34 is confusing in the recitation of "wherein targeting", which should apparently be "wherein said targeting".

Claims 35 and 72 are confusing in the recitation of "-thioethyl". It is not clear what the hyphen is meant to indicate.

Claims 59-60 are grammatically incorrect in the recitation of "is component", which should be "is a component".

Claims 146 and 153 are confusing in that they refer to enzyme types that were not elected for prosecution.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-73, 146-149 and 153-155 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Examples 5 and 6 discuss using carbohydrate-modified subtilisins to degrade concanavalin A and they also assay the results with "GG36-WT". Appar-

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ently nowhere in the instant specification is it disclosed what "GG36-WT" is, although apparently it is a wild-type enzyme of some sort. Since Figure 15 apparently shows that the modified subtilisin and the "GG36-WT" both degrade con-A, it is maintained that the disclosure of these examples does not show an improvement of the modified enzyme over the wild-type enzyme, absent a convincing showing to the contrary.

On page 93, lines 2-3, it is disclosed that "suc-AAPF-SBn" is used as substrate to assay biotin-modified subtilisin for amidase. Apparently it is not disclosed what "suc-AAPF-SBn" is so that the significance of this assay cannot be ascertained. Again "GG36-WT" is used in the assay and the significance of this is not readily obvious. In discussing Table 31 applicants state that "[t]he biotin-CMMs have an approximately four fold lower k_{cat} compared to SML-WT with the S156C-S-Biotin CMM the only exception" and that it is "about two fold lower than for SBL-WT". If one looks at the first set of numbers under the column headed " k_{cat} " then this appears to be the case (825/1940 is about 0.5) but if one looks at the set of numbers (42.7 vs. 180) then this is not true. All three columns in Table 31 have two sets of numbers and apparently it is not disclosed what these two sets of numbers are.

Claims 1-7, 11-28, 37-42, 44, 48-65, 146-148 and 153-155 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for subtilisin, does not reasonably provide enablement for the other embodiments of the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. All of the embodiments in the instant specification that have

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been shown to be operable use the enzyme subtilisin. There has not been any determination or showing that adding cysteines and/or binding the targeting moiety to the enzyme through a cysteine moiety is operable and therefore the instant claims should be limited to subtilisin. Another enzyme bound to a targeting moiety through a cysteine residue may well not have any activity.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Chandrasegaran (A). The instant reference teaches in column 7, lines 23-30 that FokI restriction endonuclease has two separate domains, a nuclease cleavage domain and a sequence recognition domain. This teaching alone would read on the instant claims as written since there is no requirement that the "enzyme" and the "targeting moiety" come from different original molecules and the phrase "targeting moiety being attached to an enzyme" reads on the intact enzyme as the two regions are attached by a peptide bond. The reference further teaches that when the cleavage domain of the enzyme is linked to

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the *Drosophila* Ultrabithorax homeodomain (Ubx) the enzyme will bind according to Ubx and cleave according to the cleavage domain. This embodiment would read on the claims when the two moieties come from different sources.

Claims 1-10, 19-29, 37-47, 56-66, 73, 146-149 and 153-155 are rejected under 35 U.S.C. 102(b) as being anticipated by Davis, et al. (C3). The instant reference teaches a *Bacillus lentus* subtilisin that has cysteine residues introduced where they were not previously and then the attachment of a carbohydrate molecule to the cysteine. It is maintained that the reference meets the requirements of the instant claims, absent a convincing showing to the contrary.

Claims 1, 2, 37 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Epenetos, et al. (N). The instant reference teaches a molecule that has a cytotoxic portion and a target cell-specific portion. It is taught that the cell specific reagent should accumulate at a higher level at the target cell than at other cells and that the purpose of their invention is to make systems that exhibit higher avidities to the selected target cells (page 2, line 29 - page 3, line 8). The joining of the two groups by the sulfur of a cysteine is taught on page 21, lines 8-18. In pages 25-29 it is taught that the "cytotoxic portion" can be an RNase or DNase (a hydrolase enzyme).

Claims 1-73, 146-149 and 153-155 are rejected under 35 U.S.C. 103(a) as being unpatentable over Epenetos, et al. (N). The instant reference is characterized *supra*. Given the teaching of the instant reference of the desirability of making a molecule with a targeting moiety and an enzyme moiety, the

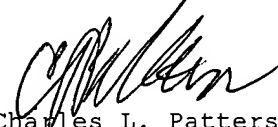
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exact site of attachment of the targeting moiety to the enzyme, the exact enzyme used and the exact targeting moiety used would have been a matter of design choice by one of ordinary skill in the art and would have been obvious, absent some unexpected results.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charles L. Patterson, Jr., PhD, whose telephone number is 703-308-1834. The examiner can normally be reached on Monday - Friday, 7:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.


Charles L. Patterson, Jr.
Primary Examiner
Art Unit 1652

Patterson
April 16, 2002